REMARKS

Claims 1, 2, 4, 7, 19-23, 26, and 42-50 are pending in the present application. No claims are amended. Claims 49 and 50 are presently withdrawn *sua sponte* by the Examiner, where Applicants traverse this withdrawal for reasons presented below, and request rejoinder and examination of Claims 49 and 50. Claims 42-48 were previously withdrawn *sua sponte* by the Examiner, and Applicants again traverse the withdrawal of Claims 42-48 and request rejoinder and examination of Claims 42-48. Thus, Claims 1, 2, 4, 7, 19-23, 26, and 42-50 are presented for examination.

Claim Rejections

Rejections over the combination of Müller *et al.* and Shu *et al.*

The present Office Action repeats *verbatim* the inconsistent statutory basis for claim rejections previously found in Office Actions mailed June 15, 2007, and August 2, 2006:

> "Claims 1, 2, 4, 6, 7, 19, 20, 21, 22 and 26 are rejected under 35 USC §102(b) as anticipated by Muller *et al.* (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) as evidenced by WO 97/01580 (a copy provided with ISR) in view of Shu *et al.*, Immunotechnology 1995 Dec;1(3-4):231-41." (OA page 2, lines 13-16; emphasis added).

Applicants will once again proceed under the assumption that the claims are being rejected under 35 USC §103(a) as allegedly obvious over Müller *et al.* in view of Shu *et al.* Applicants note that Claim 6 was cancelled by Amendment filed October 11, 2007, thereby obviating the Examiner's rejection of Claim 6.

Rejections over Müller *et al.* in view of Shu *et al.*, further in view of Plückthun and Pack

The present Office Action repeats *verbatim* the inconsistent language previously found in Office Actions mailed June 15, 2007, and August 2, 2006:

> "Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Muller *et al.*, (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) in view of Shu *et al*, (cited above) and further in view of Pluckthun and Pack (1997 Immunotechnology, vol. 3, pages 83-105) is withdrawn." (OA page 7, line 19 to page 8, line 2; emphasis added).

Applicants will once again proceed under the assumption that, despite the Examiner's statement that the rejection "is withdrawn," that the rejection stands. Applicants note that Claim 6 was cancelled by Amendment filed October 11, 2007, thereby obviating the Examiner's rejection of Claim 6.

Factual inquiries and reasoning to support a conclusion of obviousness are required for a proper determination of obviousness under 35 USC §103

"[T]he framework for objective analysis for determining obviousness under 35 USC §103(a) is based on basic factual inquiries as set forth in *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966)" (MPEP §2141(II) citing *KSR International Co. v. Teleflex Inc.*, 82 550 US __ (2007); 127 S. Ct. 1727 (2007); 82 USPQ2d 1385 (U.S. 2007), hereinafter "*KSR*"). The factual inquiries set forth by the Court are: determining the scope and content of the prior art (*see*, MPEP §§2141(II)(A) and 2141.01); ascertaining the differences between the claimed invention and the prior art (*see*, MPEP §§ 2141(II)(B) and 2141.02); and resolving the level of ordinary skill in the art (*see*, MPEP §§ 2141(II)(C) and 2141.03)

"[R]ejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (MPEP §2142, quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval)).

Here, errors in the "Graham inquiries" set forth in the present Office Action undermine the framework for determining obviousness. Furthermore, no "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" has been provided. Thus, the present claim rejections are improper and should be withdrawn.

Errors in determining the scope and content of the prior art.

It is erroneously asserted on page 4 at lines 17-19 of the Office Action, that the first monomer of the bispecificic miniantibody of Müller *et al.* allegedly comprises "CH1 domain linked via C-and/or N-terminal to two functional domains." In fact, Müller *et al.* clearly discloses in the Abstract, that CH1 is linked C-terminal to anti-EGF receptor scFv 425, the only functional domain present in the monomer, such that CH1 is <u>not</u> linked "via C-and/or N-terminal to two functional domains." Müller *et al.* only discloses one configuration for the first monomer, *i.e.* CH1 linked C-terminal to an scFv.

It is erroneously asserted on page 4 at lines 19-21 of the Office Action that the second monomer of the bispecificic miniantibody of Müller *et al.* allegedly comprises "CL1 linked via C-and/or N-terminal to two other functional domains." In fact, Müller *et al.* clearly discloses in the Abstract, that CL1 is linked C-terminal to anti-CD2 scFv M1, the only functional domain present in the monomer, such that CL1 is <u>not</u> linked "via C-and/or N-terminal to two functional domains." Müller *et al.* only discloses one configuration for the second monomer, *i.e.* CL1 linked C-terminal to an scFv.

A further error in determining the scope and content of the prior art relates to functional domains of the bispecific antibodies of Müller *et al.*. In the Office Action, it is asserted that Müller *et al.* discloses four functional domains (OA page 4 at lines 21-22), which appears to rely on an attempt to construe each VH region and each VL region of an scFv as a separate functional domain to arrive at a total of four so-called functional domains (*see*, OA page 4 at lines 17-21). In fact, Müller *et al.* only discloses two functional domains—scFv 425 and scFv M1. As Müller *et al.* state in the Introduction, the bispecific miniantibodies are "based on single-chain Fv fragments (scFv), in which the variable domain of the heavy chain (V_H) is connected by a glycine-rich linker to the variable domain of the light chain (V_L)," where each scFv is fused to a constant domain, and the constant domains "form a covalently linked heterodimer carrying two different scFv specificities." (Müller *et al.*, page 259, Introduction). That is, Müller *et al.* discloses that the functional domain that confers specificity for a target is the scFv fragment specific for that target, where each scFv includes both a VH and VL region. Because Müller *et al.* discloses scFv functional domains in bispecific miniantibodies containing only two scFv fragments, it is clearly erroneous to interpret VH and VL regions as separate functional domains and to assert that Müller *et al.* discloses four functional domains.

Errors in ascertaining the differences between the invention and the prior art

"Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." MPEP §2141.02

Prior art disclosures that teach away from the claims were not considered

Ascertaining the differences between the prior art and the claims requires that prior art must be considered in its entirety, including disclosures that teach away from the claims. (MPEP §2141.02(IV), citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983); emphasis added)

Müller *et al.* not only fails to disclose claim elements such as three functional domains having different receptor or ligand functions, or a non-immunoglobulin portion having receptor or ligand function, but also teaches away from the multifunctional compound of the claimed invention by teaching only one fixed configuration for each monomer.

Shu *et al.* not only fails to teach claim elements such as heterodimers, dimerization via constant domains, use of C_H1 or C_L constant domains, or at least three functional domains having different receptor or ligand functions, but also teaches away from the claimed

invention by teaching how to ensure homodimer formation by retaining certain amino acid sequences (Shu *et al.*, page 235, left column).

By failing to consider the disclosures in Müller *et al.* and Shu *et al.* that teach away from the claimed invention, the Examiner has failed to consider the prior art as a whole, resulting in errors in ascertaining the differences between the invention and the prior art that undermine the framework of the present claim rejections under 35 USC §103. Applicants have previously pointed out disclosures that teach away from the claimed invention, and have previously requested that these teachings be considered and addressed.

Inconsistent and arbitrary approaches to ascertaining the differences between the invention and the prior art

The framework of the present claim rejections under 35 USC §103 is further undermined by errors that result from using the construction of "functional domain" set forth in the present Office Action, to ascertain differences between the invention and the prior art.

The Examiner erroneously asserts that Müller *et al.* discloses four functional domains (OA page 4 at lines 21-22), by construing each VH region and each VL region of each scFv as a separate functional domain (see, OA page 4 at lines 17-21). As discussed above, Müller *et al.* is in fact limited to two scFv functional domains.

The invention of Claim 1 requires at least three functional domains having different receptor or ligand functions, wherein at least one functional domain comprises an scFV fragment and at least one functional domain comprises a non-immunoglobulin portion.

Applicants submit that, to use the construction of "functional domain" set forth in the present Office Action for comparing the prior art with the claimed invention, one of the scFv fragments of Müller *et al.* must be kept entire to satisfy the requirement for at least one functional domain comprising an scFv fragment, while the second scFV of Müller *et al.* must be split into its VH and VL regions to satisfy the numerical requirement for at least three functional domains having different receptor or ligand functions. The claim element requiring at least one functional domain comprising a non-immunoglobulin portion having receptor or ligand function, is still not satisfied. The error in this approach is at least twofold: (1) this approach relies on an arbitrary and inconsistent determination of the scope of the prior art with respect to functional domains disclosed in Müller *et al.*; and (2) this approach results in an arbitrary and inconsistent interpretation of the claim language with respect to functional domains recited in the claims.

No rationale to support a conclusion of obviousness has been established

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." (MPEP §§ 2142, 2143; emphasis added) In light of *KSR*, a variety of rationales may be provided to support a conclusion of obviousness under 35 USC §103 (MPEP §2143), as long as they are consistent with the proper "functional approach" to determination of obviousness set forth in *Graham.* (MPEP §2143) Despite the errors in the "Graham inquiries" discussed above, which undermine the validity of any framework underlying any reason or rationale to support a conclusion of obviousness, Applicants will nonetheless consider whether a rationale to support a conclusion of obviousness has been provided.

Applicants do not find "a clear articulation of the reason(s) why the claimed invention would have been obvious." However, Applicants will assume, based on statements in the Office Action on page 7 at lines 7-18, that the rationale of "some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention" is being relied upon for the present claim rejections.

To reject a claim based on this rationale, the Graham factual inquires must be carried out and it must be shown that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." (MPEP §2143(G), quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006)).

No teaching, suggestion, or motivation to modify references to produce the claimed invention

As discussed above, the combination of Müller *et al.* and Shu *et al.* do not teach or suggest the claimed invention. The alleged "motivation" proposed on page 7 at lines 15-18 of the Office Action, does not provide motivation to modify the heterodimeric bispecific miniantibodies of Müller *et al.* in light of the disclosure in Shu *et al.* that teaches how to make IL-2-containing homodimers with modifications to ensure homodimer formation, to produce the multifunctional compound of the present claims.

No reasonable expectation of success

Not only is there no teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference to achieve the claimed invention, but there is no reasonable expectation of success. The MPEP sets forth the basis for determining "reasonable expectation of success" as follows:

"A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. MPEP §2143.02, citing, *inter alia*, *KSR* 82 USPQ2d 1285, 1396 (2006).

As discussed above, the cited references not only fail to teach the claimed invention and fail to suggest the desirability of the claimed invention, but in fact include disclosures that teach away from the claimed invention. Thus, all the claimed elements were not known in the prior art, such that one skilled in the art could not have combined the elements, and one skilled in the art could not have predicted the results of the combination. Thus, the teachings of the prior art provide no reasonable expectation of success from modifying the teaching of Müller *et al.*, in light of the disclosures in the secondary references Shu *et al.* and Plückthun and Pack, to produce the claimed heterodimeric multifunctional compound.

Conclusion

Absent any rationale to support a conclusion of obviousness based on the cited references, no *prima facie* case of obviousness has been established and the outstanding rejection under 35 USC §103 should be withdrawn.

Request for explanation of relevance of Examiner's arguments based on construing "expressed in and secreted by a mammalian host cell"

Applicants note that the claim rejections in the Office Action once again include arguments based on construing "expressed in and secreted by a mammalian host cell" to make statements concerning product by process claims (OA page 5 final paragraph, to page 6 entire page). In the Remarks made in past Amendments, Applicants have repeatedly pointed out that this claim element was not at issue and was not being argued. Applicants again point out that this claim element is not presently at issue and is not being argued in the present Amendment. Applicants once again request an explanation of the relevance of this argument to the current claim rejections.

Traversal of Examiner's *sua sponte* Withdrawal of Claims 42 to 50

Applicants traverse the Examiner *sua sponte* withdrawal of Claims 42-50, on grounds that the Examiner erred in applying the Applicants' election in response to the Restriction

Requirement mailed November 18, 2003, such that Claims 42-50 are incorrectly withdrawn from examination. Applicants request examination of Claims 42-50.

When the claims of Group 8 were elected, Applicants understood that correct application of Office restriction practice would result in examination of all claims reciting a multifunctional compound "comprising an antigen binding region specific for a tumor-associated antigen," including claims reciting specific embodiments. Applicants further understood that, because some claims to multifunctional compounds recite additional functional domains besides an antigen binding region specific for a tumor-associated antigen, correct application of Office restriction practice could result in initial examination in part of such claims, limited to examination of the recital of a functional domain comprising an antigen binding region specific for a tumor-associated antigen. Election of Group 8 does not preclude entry and examination of new claims that recite embodiments of the elected antigen binding region specific for a tumor associated antigen. Therefore, Claims 42-50 should be rejoined and examined.

Traversal of Examiner's withdrawal of Claims 49 and 50

Applicants traverse the Examiner's *sua sponte* withdrawal of Claims 49 and 50, and request rejoinder and examination of Claims 49 and 50. Claims 49 and 50, presented by Amendment filed October 11, 2007, recite specific embodiments of the antigen binding region specific for a tumor associated antigen, namely, scFv fragments of the human anti-human EpCAM antibody HD70. Claims 49 and 50 are to undergo initial examination in part, pursuant to the election of Group 8, for their recital of embodiments of a functional domain comprising an antigen binding region specific for a tumor associated antigen. Therefore, Claims 49 and 50 should be rejoined and examined.

Traversal of Examiner's withdrawal of Claims 42-48

Applicants again traverse the Examiner's *sua sponte* withdrawal of Claims 42-48, presented by Amendment filed March 26, 2007, and request rejoinder and examination of Claims 42-48.

Claims 42-43 recite specific embodiments of the antigen binding region specific for a tumor associated antigen, *per* Group 8. Claims 44-48 depend from Claim 7 reciting an antigen binding region specific for a tumor associated antigen. Thus, Claims 42-48 are to undergo examination in part, pursuant to the election of Group 8, for their recital of a functional domain comprising an antigen binding region specific for a tumor associated antigen. Therefore, Claims 42-48 should be rejoined and examined.

CONCLUSION

Claims 1, 2, 4, 7, 19-23, 26, and 42-50 are pending and presented for examination. Applicants request that Claims 1, 2, 4, 7, 19-23, 26, and 42-50 be found in condition for allowance in light of the remarks presented herein.

This Amendment is being filed within two months of the mailing date of the outstanding final Office Action.

Applicants believe no fees are due. If any fees are due, please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any overpayments to the above-referenced Deposit Account.

Respectfully submitted,

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